Current perspectives

Inhaled corticosteroid dosing: Double for nothing?

H. William Kelly, PharmD *Albuquerque, NM*

Two recent trials from the National Heart, Lung, and Blood Institute's asthma clinical trials networks raise a concern about using double the dose of an inhaled corticosteroid (ICS) as a positive control arm in clinical trials of add-on therapy. The literature evaluating the response to doubling the dose of an ICS is briefly reviewed. The vast majority of studies do not demonstrate a significant positive benefit from doubling the dose of an ICS but do show improvement with 4-fold increases that is equal to or greater than that of add-on long-acting bronchodilators. It is recommended that doubling the dose of an ICS no longer be considered a positive comparator arm in clinical trials, although it might be beneficial in individual patients. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

Key words: *Asthma, clinical trials, inhaled corticosteroids, long-acting β_2-agonist, outcomes*

Abbreviations used
BADGER: Best Add-on Therapy Giving Effective Responses
ICS: Inhaled corticosteroid
LABA: Long-acting β_2-agonist
PEF: Peak expiratory flow
TALC: Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower dose of Inhaled Corticosteroid

"Curiouser and curiouser!" cried Alice.

—Lewis Carroll.

Two recent publications by the adult and pediatric asthma clinical research networks evaluating add-on therapy to inhaled corticosteroids (ICSs) raised my curiosity about the comparator arm of doubling the dose of an ICS.[1,2] In the first study (Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid [TALC]), a 3-way crossover, the addition of tiotropium bromide was compared with doubling the dose of the ICS in a superiority analysis and the addition of salmeterol in a noninferiority analysis.[1] Tiotropium bromide was found to be superior to doubling the dose of the ICS (160 vs 320 μg/d beclomethasone dipropionate administered through a hydrofluoroalkane-propelled metered-dose inhaler). Although a new finding, this was not particularly surprising because the primary outcome was improvement in lung function as measured by improvement in peak expiratory flow (PEF), and we have had 16 years of literature demonstrating improvement in lung function when adding long-acting bronchodilators, albeit long-acting β_2-agonists (LABAs), to patients whose symptoms were incompletely controlled with ICSs.[3,4] In addition, they demonstrated greater improvement for tiotropium bromide in other measures from the impairment domain: symptom scores, asthma control days, and Asthma Control Questionnaire results. However, the authors provided results seldom seen in the pantheon of add-on literature by comparing each 14-week treatment with the 4-week run-in baseline period on low-dose ICSs.

From the time of the first study by Greening et al,[4] most trials comparing add-on therapy with a LABA with an increased dose of ICS, usually doubling, reported the analysis comparing the differences in outcomes between treatments but not the significance of changes from baseline of each therapy. This method of reporting does not allow the reader to determine whether the arm of the study producing the lesser effect actually produced an improvement in the outcomes. For a more complete list of references, please see this article's Online Repository at www.jacionline.org.[5]

Peters et al[1] reported no significant differences from baseline from doubling the ICS dose with the exception of the proportion of asthma control days ($P = .02$), and the PEF measures and mean daily symptom scores worsened numerically. This finding should also come as little surprise because of the wealth of information in the literature demonstrating little to no difference in efficacy from doubling the dose of an ICS (for a complete listing, see this article's Online Repository).[6-8] Indeed, Greening et al[4] reported that increasing the dose of beclomethasone dipropionate, in this case 2.5-fold, resulted in an increase in morning PEF but not evening PEF. However, the increase in mean morning PEF from baseline in the group receiving a higher ICS dose ranged from 5 to 15 L/min over the 21 weeks, which was less than the 20 L/min difference that the study was powered to detect. In fact, 45% of patients experienced a decrease or no change in morning PEF.

In the most significant study (OPTIMA) addressing this issue, O'Byrne et al[9] compared doubling the dose of budesonide from 200 to 400 μg/d in 634 patients with mild-to-moderate persistent asthma for 1 year after a 4-week run-in period with the main outcomes of time to first major exacerbation (requiring oral corticosteroids) and poorly controlled asthma days. Doubling the dose of the ICS produced no significant improvement in the main outcomes, with mixed results in the other impairment domains. Patients in the 400 μg/d group had significantly lower morning PEFs ($P = .042$) than the 200 μg/d group but higher FEV_1 values

From the Department of Pediatrics, University of New Mexico.

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Reprint requests: H. William Kelly, PharmD, Department of Pediatrics, Pediatrics/Pulmonary, MSC10-5590, 1 University of New Mexico, Albuquerque, NM 87131-0001. E-mail: hwkelly@salud.unm.edu.

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($P = .02$). There were no significant differences in nights with awakenings or the number of rescue inhalations, but there was a decrease of 3.1% in days with symptoms ($P = .017$) for the 400 μg/d group. The small differences were likely statistically significant because of the large number of patients in the study. The evaluation of exacerbations complements the study by adding the risk domain that many of the studies do not include because of insufficient duration and too few patients.

In a meta-analysis of studies assessing the effect of higher doses of ICSs on reducing the risk of exacerbation, only 2 studies demonstrated a reduction in exacerbations, and they both used a 4-fold increment in dosing.[8] In the largest study Pauwels et al[10] compared budesonide at 200 and 800 μg/d in 427 patients with moderate persistent asthma treated for 1 year after a 4-week run-in period. They also included 2 other comparator groups with the same ICS doses and the addition of the LABA formoterol. They reported a 49% reduction in exacerbations between the low-dose and higher-dose budesonide ($P < .001$), which was greater than the 26% reduction produced by adding the LABA ($P = .03$). The reduction in exacerbations from the higher dose of ICS was accompanied by significant improvements in impairment measures: nighttime awakenings, rescue inhalations, nighttime and daytime symptom scores, and episode-free days. Of note, 800 μg/d budesonide is in the medium dose range suggested by the National Asthma Education and Prevention Program's dosing chart for ICSs, and therefore one can go from a low-dose to a medium-dose ICS and obtain significant benefit.[3] Parallel dose-ranging trials with a single ICS performed for marketing approval show similar results in that there is no difference between doubling doses but there is increased efficacy for a 4-fold increase in dose (for complete references, see this article's Online Repository).[11] These studies often report a statistically significant trend for dose response, but that trend is really driven by the significant differences between the lowest dose and the 4-fold increase in these studies.[6,11]

Manufacturers have obtained marketing approval of multiple doses of single-strength inhaler devices or multiple strengths of the device by studying them in different populations (ie, by using the lowest strengths and doses in asthmatic patients receiving only as-needed short-acting β_2-agonists and the higher doses or strengths in those patients already receiving ICSs and other markers of greater severity, such as lower lung function or previous exacerbations). Unfortunately, in these studies we do not know whether the lower dose would have performed as well as the higher dose. This is exemplified by large parallel trials of the newer ICSs, such as ciclesonide, that do not demonstrate significant differences even between 4-fold differences in dose in some studies when the entry criteria are the same for all patients.[12] This has also occurred in a number of single-center clinical trials evaluating specific aspects of airway inflammation, such as induced sputum and bronchial provocation (for more details, see this article's Online Repository). Finally, the magnitude of difference in the outcomes of FEV_1, proportion of symptom-free days, and rescue bronchodilator use were very similar in 2 Cochrane Library reviews, one comparing the addition of a LABA or placebo to a baseline ICS and the other evaluating the addition of a LABA to an increased ICS dose.[5,13]

If we have known for the last 10 years that doubling the dose of an ICS is essentially no different than not changing the dose or adding placebo, why do we (the collective research community) continue to use it as a comparator arm in add-on clinical trials ("curiouser and curiouser")? For one, the entry criteria for these studies usually include a run-in period to establish that the patients' symptoms are not well controlled or completely controlled with a low-dose ICS. As clinicians, there is an ethical dilemma about placebo use in these patients, and doubling the dose is more likely to receive institutional review board approval. From the perspective of the manufacturer of the add-on product, one is more likely to demonstrate improved outcome from the add-on product if the dose of ICS is just doubled. From a general safety perspective, if starting patients close to or in the medium dose range, a 4-fold increase in ICS dose would enter the high dose range and increase the risk of measurable systemic effects. However, if the 4-fold increment in dose significantly increased the risk of adverse effects, that is knowledge that clinicians could use to determine the course of action for their patients to determine the preferred therapy.

This brings us to the other study from the Childhood Asthma Research and Education Network that compared the addition of a LABA with the addition of montelukast and a 2.5-fold increased dose of ICS in 182 children with persistent asthma that is not well controlled with a low-dose ICS (ie, 200 μg/d fluticasone propionate; the Best Add-on Therapy Giving Effective Responses [BADGER] study).[2] This was also a 3-way crossover trial but used a relatively new analysis in that it used a composite hierarchical outcome (in order: exacerbations, 1 additional day per month of asthma control days, and ≥5% difference in FEV_1) and preference statistical analysis to determine the differential response to the 3 treatments. This analysis allows the clinician to determine not only which therapy is generally better but which therapy is better in a higher proportion of patients. By then assessing predictors of individual responses or preferences, this moves us closer to being able to individualize therapy. The authors reported greater proportions preferring LABA step-up therapy to montelukast (52% vs 34%, $P = .02$) and ICS step-up therapy (54% vs 32%, $P = .004$) with no difference between the proportion preferring ICSs and montelukast. On this basis, the accompanying editorial suggested that physicians might want to start with the less-preferred therapies to avoid risks associated with LABA use. However, the underlying assumption of a preference analysis is that all of the treatment arms have been shown to be effective; otherwise, one should have a placebo arm so that randomly occurring differences in preference can be quantified.

The Childhood Asthma Research and Education Network undertook the BADGER study because there were few data to compare the relative effectiveness of various step-up strategies in children. Although there were a number of trials establishing the efficacy of the addition of LABAs to ICSs,[5] there were minimal data to suggest the effectiveness of doubling the dose of ICS or add-on montelukast in that age group, particularly for the outcome measures they used.[11,14-16]

Shapiro et al[11] reported a significant difference in FEV_1 (mean difference, 4.2%) over 12 weeks between 200 and 800 μg/d budesonide but not between 400 and 800 μg/d budesonide (mean difference, 0.4%) in 404 children 6 to 18 years of age. They observed similar findings for daytime symptom scores, with the only significant difference found between 200 and 800 μg/d.

Verberne et al[14] compared the addition of salmeterol with doubling the dose of chlorofluorocarbon-propelled beclomethasone dipropionate from 400 to 800 μg/d in 177 children with moderate asthma over a 1-year period. Unlike many studies, they continued the low-dose ICS in 1 arm of the study. They found no difference between the low- and high-dose ICS arms for improvement in

FEV_1, exacerbations, or symptom scores, nor did they find an improvement with the addition of salmeterol, but they did report decreased growth in the higher-dose ICS arm compared with the other study arms.

A more recent study by the same group that was published after the BADGER study compared 400 μg/d fluticasone propionate with 200 μg/d fluticasone propionate plus 100 μg/d salmeterol in 158 children aged 6 to 16 years with uncontrolled symptoms on 4 weeks of 200 μg/d fluticasone propionate.[15] They reported no difference between treatments over 26 weeks and no significant improvement from baseline in lung function. However, they did demonstrate a significant 25% improvement in symptom-free days with both therapies over baseline.

It is possible that the symptom-free days used in OPTIMA or the asthma control days used in the BADGER and TALC studies are more sensitive measures of therapeutic effect and differential and dose response in both children and adults with relatively normal lung function. Unfortunately, the BADGER study did not report which of the hierarchic outcomes drove the differential response. Simons et al[16] compared the addition of montelukast or placebo to 400 μg/d budesonide in a crossover trial in 279 children 6 to 14 years of age with moderate asthma. They reported no significant difference in FEV_1 in the intention-to-treat population but a significant ($P = .01$) 2% mean difference from placebo in the per-protocol population. There was no difference in exacerbations, and asthma control days were not measured. Thus another perspective of the results from the BADGER study would be that the preference rates exhibited by the 2 alternate treatments of adding montelukast or doubling the corticosteroid dose just represent the random preference rate had nothing (with only placebo added) been done.

The dose-response data for ICSs in infants and young children less than 5 year of age are even more tenuous (for more information, see this article's Online Repository). A review of the pivotal trials for budesonide nebulizer suspension found that once the dose exceeded 0.25 mg once daily, which was inconsistently better than placebo, there were no significant differences in efficacy from doses of 0.5 to 1.0 mg/d. Similar results have been reported from studies of chlorofluorocarbon-propelled fluticasone propionate administered through a valved holding chamber with a mask in which 100 μg/d (88 μg/d as labeled by the US Food and Drug Administration) did not produce consistent efficacy over placebo but 200 μg/d did. No dose-response studies with the newer hydrofluoroalkane-propelled ICSs have been completed in this population, nor have many efficacy and safety trials been performed. These are badly needed.

Finally, what does this mean for the practitioner? Should they not bother doubling the dose of an ICS if patients' symptoms are uncontrolled with the current dose? Few studies have been designed to assess the potential for individual patient responses. However, 2 studies have looked at this issue.

Szefler et al[17] performed a dose-escalation study of beclomethasone dipropionate (n = 12) and fluticasone propionate (n = 9) with FEV_1 and bronchial responsiveness to methacholine as outcome measures. The first dose escalation was 4-fold and the next was 2-fold, representing the low, medium, and high doses from the guidelines. There were 1 to 2 patients in each group who demonstrated improvement in the end point after the doubling dose.

Bateman et al,[18] in the much larger (n = 3421) Gaining Optimal Asthma Control study, compared the use of escalating doses of combination ICS/LABA therapy with ICS monotherapy in establishing well-controlled and completely controlled asthma. The increases in the dose of fluticasone propionate were 200, 500, and 1000 μg/d. In the 550 patients who entered the study receiving no baseline ICS therapy and who received monotherapy, 39% achieved well-controlled status, but an additional 18% achieved well-controlled status with the first doubling of the dose, and then an additional 5% achieved well-controlled status with the second doubling dose. Similar findings were reported for the doubling of doses in the 577 patients who entered the study receiving low-dose ICSs.

Thus it is clearly possible to improve asthma control in individual patients with mild-to-moderate asthma by doubling the dose of ICS from low to medium and from medium to high. The problem as an arm in comparative clinical trials is that the largest proportion of patients achieve well-controlled status at low doses of ICSs, and in those who do not, only an additional 15% to 20% will have improved control with doubling of the dose. This is an insufficient number of patients with improvement to detect a significant difference from doubling the dose, particularly when up to 50% of patients might show a decrease in lung function or worsening symptoms after the change.[4] However, it is possible to enhance the sensitivity of the response to doubling the dose of ICS as a comparator arm in clinical trials.

Busse et al[19] compared the combination of 100 μg of fluticasone propionate/50 μg of salmeterol twice daily with the higher dose of 250 μg of fluticasone propionate twice daily. However, they used a unique 3-part run-in design in which patients first established well-controlled asthma on 250 μg twice daily and then decreased the dose to 100 μg twice daily. Those patients who lost well-controlled status on the lower dose then were enrolled into the third part of the run-in study, where they once again needed to demonstrate well-controlled status. In using this type of run-in method, the investigators lost 27% of those enrolled in the first run-in period primarily because they did not show deterioration on the lower fluticasone dose. This approach obviously extends the run-in period for studies and requires a larger initial enrollment that is lost but could serve as a model for enhancing the sensitivity of comparative clinical trials.

In conclusion, large well-controlled clinical trials have consistently failed to demonstrate that doubling the dose of ICS in those patients whose symptoms continue to be uncontrolled with low- and medium-dose ICSs consistently produce any further benefit. This is likely due to the small percentage of patients who do show an improved response. Therefore doubling the dose of ICS is often no better than adding placebo as a comparator arm in clinical trials. Although this does not pertain to dose adjustment in the patient who might respond to doubling of the dose, we need to begin to question the validity of using doubling doses of ICSs as a true positive control arm in clinical trials. A 4-fold increase in ICS dose has been demonstrated to be effective and has exceeded the effect of adding LABAs to ICSs for reducing exacerbations and improving asthma control.[10] Thus we should not conclude that increasing the dose of ICS is necessarily less effective than adding a LABA, although the ICS/LABA combination can produce similar control at lower ICS doses. Finally, demonstrating that any new add-on therapy is as good as doubling the dose of an ICS demonstrates that it is as good as doing nothing unless it can be shown to improve outcomes over at least a 4-week baseline.

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